Palliative thoracic radiotherapy is a cornerstone of any radiation oncology practice; older estimates from the United Kingdom suggest that 10% to 25% of a typical radiation oncologist's practice deals with lung-related issues, with a high proportion of these palliative in nature.[1] A meta-analysis and guideline-based recommendations indicate that higher doses of palliative radiotherapy (such as 30 Gy in 10 fractions) translate to a modest benefit in overall survival when compared with lower biological effective dose regimens.[2,3] Although it is difficult to retrospectively analyze the decision making in cases where lower doses of radiotherapy were used in our study, we do note that approximately half of patients (48%) received at least 20 Gy. From a practical point of view, a careful balance must be struck between the urgency of treatment and the ability to deliver higher doses of radiotherapy safely. Common palliative dose fractionation schemes (such as 8, 20, or 30 Gy in 1, 5, and 10 fractions, respectively) can be planned and delivered on the same day as consultation. Conversely, any benefit in local control derived from higher doses, using intensity-modulated radiotherapy or image-guided radiotherapy approaches, may be mitigated by delays incurred in a lengthier treatment-planning process.

Severe malignant airway obstruction can present dramatically and result in acute dyspnea and respiratory collapse. Often these patients are urgently intubated and only afterward questions surrounding best management, including a reasonable duration of trialing mechanical ventilation arise. We considered abstracting ventilation data, but ventilation strategies often changed during treatment and were heterogenous. As with any intervention where the primary goal is palliation, assuring that functional status is improved by the intervention is paramount. Although we did not directly abstract quality of life or performance status data, the fact that approximately all extubated patients were discharged home, with some receiving chemotherapy thereafter, can be considered surrogates of their improved functional status.

Although a randomized control trial to demonstrate the efficacy of radiotherapy over best supportive care in this patient population would be ideal, given these patients' grave clinical situation and the suggestion that radiotherapy *could* be of benefit, it would be difficult to establish equipoise to run such a trial. Going forward, we propose that institutions using radiotherapy in this setting develop guidelines with input from oncologists, intensivists, and allied health professionals. Just as important as identifying endpoints relevant to each multidisciplinary stakeholder, a guideline would set standards and policies to improve patient safety during transportation and minimize the time away from the intensive care unit. Although data from such an initiative would be intriguing, in the interim we would encourage others to report their experience in using radiotherapy in this clinical setting or to discuss obstacles that currently prevent them from doing so.

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Coexistence of Tyrosine Kinase Inhibitor-Sensitizing and Resistant *EGFR* Mutations in an Untreated Lung Adenocarcinoma Patient and Response to Erlotinib

To the Editor:

A 50-year-old asian man with a remote history of light smoking (half a pack per day × 4 years) presented to the orthopedic clinic with several months of progressively worsening right hip pain. A radiograph showed a lytic lesion in the right acetabulum with soft-tissue involvement. Computed topography (CT)-guided biopsy revealed a moderately differentiated adenocarcinoma, positive for TTF-1 and CK7 and negative for CK20 by immunohistochemistry. CT scan revealed a 10 mm irregular nodule in the apex of the left lung with hilar and mediastinal lymphadenopathy. The patient was diagnosed with metastatic lung adenocarcinoma and staged as IVB. *EGFR* mutation analysis was performed using massively parallel sequencing using the Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies, Carlsbad, CA). A compound heterozygous mutation in exon 19 (*c.2240T>C*, p.L747S and *c.2246_2260de15*, p.A750_K754del) was identified (Fig. 1) and the result was confirmed by Sanger sequencing (Fig. 2). The two mutations were also found to be allelic as shown in Figure 1. Given the positive family history of lung cancer (father; no detailed

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FIGURE 1. Identification of *EGFR* exon 19 compound mutation by massively parallel sequencing. Genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue. *EGFR* mutation analysis was performed using the Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies, Carlsbad, CA) at our molecular pathology laboratory. The hollow arrow indicates point mutation and the solid arrow indicates the region of the15 base-pair deletion.

information available), *EGFR* mutation analysis was performed on the patient's peripheral blood to rule out a germline mutation. No mutation was found. The patient was treated with Erlotinib, 150 mg/d, in conjunction with palliative radiation therapy directed to his right acetabulum. He developed non-itching rashes on his nose and forehead and had loose stools, but otherwise tolerated the therapy. Follow-up chest CT after 2 months of Erlotinib showed interval decrease in the size of the lung nodule (Fig. 3), but slight increase in the size of a mediastinal lymph node. At 6-month follow-up, CT showed no interval tumor growth and radiograph showed improvement of the hip lesion. The patient had almost no hip pain, his energy level had increased, and he was able to go back to work full time.

Compound mutations comprise up to 14% of mutations identified in the tyrosine kinase domain (exons 18–21) of the *EGFR* gene.[1] More than one-third of the compound mutations found before therapy involve one of five amino

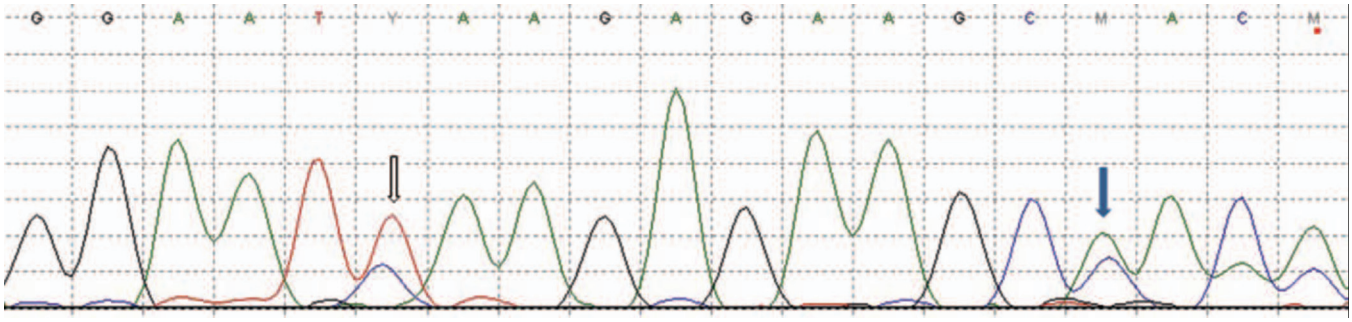

FIGURE 2. Identification of *EGFR* exon 19 compound mutation by Sanger sequencing. Exons18-21 of the *EGFR* gene was polymerase chain reaction amplified and Sanger sequencing was performed. The hollow arrow indicates the *c.2240T>C* point mutation and the solid arrow marks the beginning of the15 base-pair deletion (*c.2246_2260de15*).

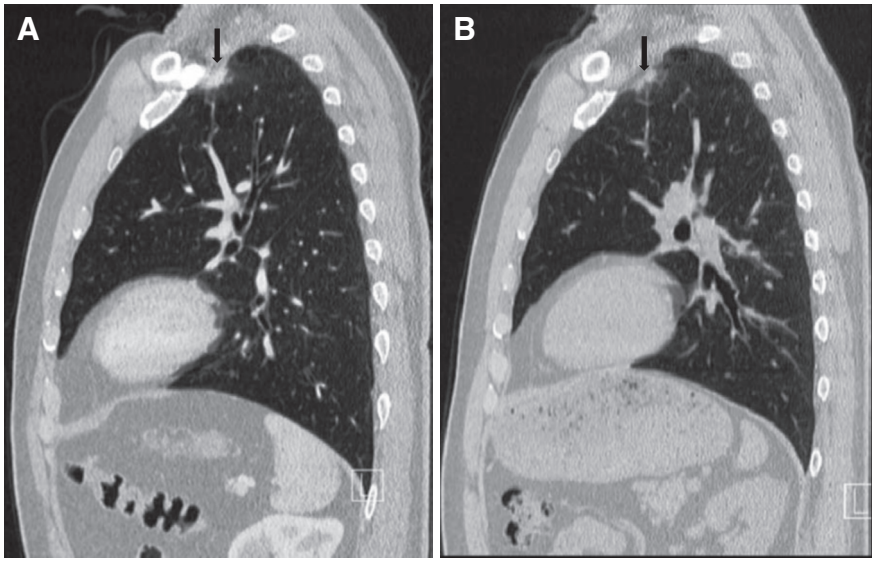

FIGURE 3. Computed Tomography images of the initial presentation (*A*) and 2 months post-Erlotinib treatment (*B*) of the lung nodule.

acids: E709, G719, S768, T790, and L858.[2] Exon 19 deletions are less frequently found in compound mutations in untreated patients.[3] The p.L747S mutation is also rare with only seven cases being reported in the COSMIC database (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic). The compound p.L747S and p.A750_K754del mutation was only reported in one case in the literature, in a 73-year-old asian woman with unknown smoking status or therapy information.[2] Exon 19 deletions are known to be associated with sensitivity to tyrosine kinase inhibitor (TKI) and tumors harboring p.L747S mutation are TKI resistant.[4] We are reporting for the first time the Erlotinib response in a TKI-naive patient with a compound TKI-resistant and sensitive mutation. The patient is currently in remission and still receiving Erlotinib therapy. It should be noted that cells carrying p.L747S mutation may become predominate after initial TKI response because of clonal selection of tumor cells carrying this p.L747S-resistant mutation.

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To the Editor:

I congratulate Professor Yang and his colleagues in successfully performed a multinational large-scale molecular epidemiology in the frequency of activating *EGFR* mutations in treatment-naïve advanced adenocarcinoma of the lung in seven Asian countries and several Asian ethnic groups. Vietnamese patients had the highest incidence of *EGFR* mutations, whereas Indian patients had the lowest while about half of Filipino patients harbored *EGFR* mutations.[1] In addition, general epidemiology parameters were comprehensively collected from all seven countries including detailed smoking status.[1] We have previously published that Vietnamese-American females had the highest percentages (65.5%) of never smokers among the the six Asian-American subgroups analyzed, whereas Japanese-American female NSCLC patients had the lowest proportion (19.3%) of never smokers and about half of Filipino-American female NSCLC patients were never-smokers.[2] Besides activating *EGFR* mutations, others targetable driver mutations such as rearrangement in *ALK, ROS1,* and *RET* are also found primarily in never-smokers. Therefore, would Professor Yang and his colleagues be able to provide the breakdown by smoking status among patients within each individual country and further breakdown of smoking status by sex within each of the seven countries.

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